STUDY PROTOCOL

IRBMED #: **HUM00045266**

PROJECT TITLE: **Psychosocial pain management during addictions treatment to improve outcomes I**

Working TITLE: **The STAR Study**

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I. Objective

The proposed project will determine the efficacy of a cognitive-behavioral pain management intervention targeting individuals with co-occurring pain and substance use disorders who will be recruited from a residential treatment center. This proposed efficacy study will provide crucial data on a brief, innovative method designed to improve outcomes in the large numbers of individuals with both substance use disorders and chronic pain.

II. Specific Aims

Chronic pain among individuals who misuse drugs or alcohol is a common and critically important problem that is rarely managed appropriately. The estimated rates of chronic pain in Substance Use Disorder (SUD) treatment are as high as 60%. Chronic pain is seldom successfully addressed in SUD treatment settings because of a limited understanding of the problem and a lack of effective intervention strategies. A clear and urgent need exists for the study of effective alternatives to the use of opiate pain medications in those treated for SUDs who also have pain because of: (1) the potential for abuse and diversion of opiate medications by patients in SUD treatment; and (2) recent evidence that untreated pain may undermine the effectiveness of standard treatments for SUDs.

An important potential strategy to address this problem is the use of Cognitive Behavioral Therapy (CBT) to manage pain and decrease substance misuse. Psychosocial interventions such as CBT have demonstrated efficacy for reducing pain and improving functioning for a broad spectrum of pain-related conditions. However, this form of treatment has not been explicitly tested in patients with co-occurring substance use disorders. Additionally, although pain is common in both men and women, most studies have lacked sufficient power to test the effect of interventions separately in men and women. The present intervention is designed to integrate CBT for pain and CBT for SUDs with the primary goal of improving pain- and substance-related outcomes. We will test the efficacy of this modified protocol on both men and women in this understudied patient population.

We will conduct a randomized controlled efficacy trial of a group-based intervention that integrates CBT for pain and SUDs compared to a Supportive Psychoeducation Control (SPC) group in a sample of patients in residential SUD treatment with co-occurring chronic pain. The proposed study is a Stage II trial which is appropriate because of: 1) our promising pilot data on the potential effectiveness of the intervention (see Preliminary Studies); and 2) the strength of the existing data on the efficacy of similar interventions in those without SUDs. Up to a total of 550 patients (275 male and 275 female) with current pain rated as moderately severe or greater and comorbid drug or alcohol use disorder(s) will be recruited from a large residential SUD treatment program. These participants will be randomly assigned to either a 4-week (8-session) group of integrated CBT for pain and SUDs or a 4-week (8-session) SPC group. All participants will be re-assessed immediately post-treatment (1 month) and again at 3, 6, and 12 months post-intervention.

The Specific Aims are:

1. To determine, within each gender, whether SUD patients with chronic pain who are randomly assigned to a CBT intervention for pain and SUDs have significantly greater reductions in pain level, pain tolerance, and pain-related disability compared to those assigned to a SPC (control) condition at 1-month (immediately post-intervention), and at 3-, 6- and 12-month follow-up.

2. To determine, within each gender, whether SUD patients with chronic pain randomly assigned to a CBT intervention for pain and SUDs have significantly reduced frequency of illicit drug use, alcohol use, and opioid medication misuse compared to those in the SPC condition at 3-, 6- and 12-month follow-up.

The **secondary aims:**

1. To explore whether reduced pain level and pain tolerance at the end of intervention (i.e. the 1-month assessment) mediate the effect of treatment assignment (CBT vs. SPC) on frequency of illicit drug use, alcohol use, and opioid medication misuse at 3-, 6- and 12-month follow-up.

2. To explore whether increased self-efficacy, motivation, effective coping, and acceptance of pain during intervention (from baseline to 1-month) mediate the effect of treatment assignment (CBT vs. SPC) on frequency of illicit drug use, alcohol use, and opioid medication misuse at 3-, 6- and 12-month follow-up.

3. To determine whether SUD patients with chronic pain who are randomly assigned to a CBT intervention for pain and SUDs have significant reductions in HIV risk behaviors *and depression* compared to those assigned to the SPC condition at 3-, 6- and 12-month follow-up.

This project is ***significant*** because improved treatment of pain in those with SUDs could result in enhanced quality of life and improved pain-related, substance use, and other health outcomes. Compelling data on the efficacy of intervention strategies for co-occurring pain and substance misuse are non-existent[1]. Evaluating a psychosocial intervention for pain and substance use that can be delivered during a SUD treatment episode would significantly extend available treatment options for the large numbers of patients with pain seen by SUD treatment providers. The project is ***innovative*** because it will determine the efficacy of an evidence-based psychosocial pain management approach in men and women from a large and diverse residential addiction treatment program. Empirically-based treatments exist for pain but these have been underutilized and understudied in this population. Given promising preliminary data using the proposed intervention strategy, as well as the demonstrated efficacy of similar interventions in other patient populations, the next logical step to optimize outcomes for the large proportion of patients with chronic pain and co-occurring SUDs is to conduct a Stage II randomized controlled trial that will potentially provide clinicians with new methods to address a serious and pervasive problem in SUD patients.

III. Background/Significance

Chronic pain is common in the general population of the United States, with over a quarter of adults reporting some form of persistent and/or significant pain [2-4]. In addition to being associated with many physical health-related problems [5, 6] and significant loss of productivity and quality of life [7, 8], the presence of chronic pain is also linked to a higher prevalence of numerous psychiatric conditions [9-12]. In particular, chronic non-cancer pain and substance use disorders (SUDs) frequently co-occur in community and clinical settings [13-16].

The estimated rates of chronic pain in SUD treatment vary substantially, from approximately 16% to over 60%, depending on the type of pain examined and the clinical setting [16-22]. For patients seen in SUD treatment, those with pain-related problems tend to report more depression, anxiety, suicidal ideation, greater functional limitations, and more extensive use of drugs and alcohol [16, 18-21] than those without chronic pain.

<u>Lack of effective treatments for chronic pain in those with substance use disorders</u>

Existing practice guidelines have increasingly emphasized the importance of assessing and treating chronic non-cancer pain [23, 24]. In practice, this often involves the prescription of opioid pain medications [23, 25]. Over the past decade, the rate of prescription of opioids has increased dramatically [26, 27]. However, the use of these medications is controversial in all patients because of the lack of data on the long-term efficacy of

opioids to treat pain, and the added concern that long-term opioid use may be associated with a reduced tolerance for pain[28]. These concerns are magnified in individuals with a history of alcohol or drug misuse because of a potential for abuse and diversion of opioid medications [23, 29, 30]. Compton and Volkow [31] noted that one of the primary questions facing clinicians and researchers is "how should one treat pain in persons who have a history of addiction or those who already exhibit signs of addiction?" (pg.106).

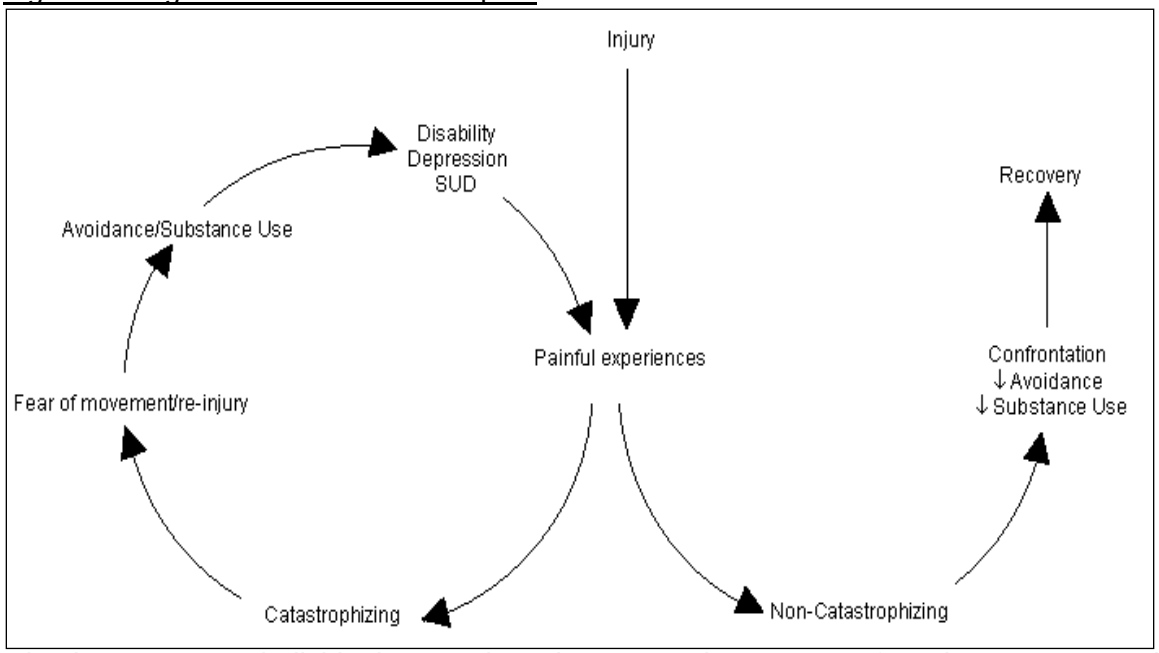
These concerns are particularly pressing in SUD treatment settings where, by definition, virtually all patients have a recent history of problematic substance use, and a large proportion of these patients also have difficulties with chronic pain [13, 16, 18, 21, 32, 33]. Recently, Samet and Walley [34] argued that challenges surrounding pain management are so central to the delivery of successful SUD treatment that proficiency in pain management should be added to the core competencies required for certification in Addictions Medicine.

The presence of chronic pain is associated with a poorer course of post-treatment outcomes following SUD treatment [19]. For example, a recent study of non-opioid dependent patients treated for SUDs found that persistent pain was present in 33% of the sample, and those with pain were more likely to drop out of treatment early and were less likely to be abstinent at 12-month follow-up than those without pain [17]. In theory, these outcomes could be improved through better management of pain in SUD patients. However, as noted previously, little guidance exists for *how* to treat this pain.

Cognitive theory of pain and substance use

A psychosocial model of pain and substance use provides an initial framework for understanding the determinants of chronic pain as well as potential areas of focus for treatment [35]. Although, in many cases, the causes of acute pain are biological, the maintenance of chronic pain and its associated problems reflect a mixture of perceptual, affective, behavioral and physical responses.

Figure 1: Cognitive model of chronic pain



The fear-avoidance model of chronic pain was proposed by Lethem and colleagues [36] and this theory has been expanded and adapted over time to apply to many different types of pain [37, 38].

Within this approach (depicted in the left side of Figure 1), a cycle of negative outcomes is observed when a specific painful stimulus causes an individual to consistently assume the worst – referred to as *catastrophizing*. This cognitive component of the model leads, in turn, to greater fear of re-injury which increases the likelihood of avoidance of activities and the use of maladaptive coping strategies. *The use of maladaptive coping strategies serves as the link between fear and more chronic negative outcomes such as disability and depression*. For individuals with SUDs, the maladaptive coping strategies often involve the use/misuse of alcohol or illicit substances or overuse of opioid medications [10]. This model has been used extensively for the past 25 years, as part of most multidimensional treatments for pain, and a recent factor analysis of two large samples of pain patients found broad support for this model [39].

Cognitive Behavioral Therapy for improving pain management in those with SUDs

Cognitive behavioral interventions for pain are based on a biopsychosocial perspective [35, 40]. CBT is directly designed to address the factors leading to poorer functioning and maintenance of the negative cycle

characterized by the fear-avoidance model [41, 42]. The "exit strategy" from this negative cycle is represented on the right-hand side of Figure 1. Within this approach, a shift in perception of pain (i.e., non-catastrophic thinking) decreases fear and facilitates increased activity and recovery of functioning. Thus, when a change in perception is coupled with improved coping behaviors (e.g., decreased substance use), negative outcomes are reduced. Recent versions of CBT for pain have emphasized pain *acceptance* as an important target for therapy [43-45]. The overarching goal of CBT for pain is to assist the patient in the development of an adaptive problem-solving approach based on a conceptualization of pain as controllable and/or tolerable.

The proposed study uses a cognitive behavioral approach for pain management with an emphasis on acceptance of chronic pain that has been modified for substance users. Cognitive behavioral interventions specifically targeting SUDs are widely used and have solid efficacy [46-48]. Integrating aspects of CBT for SUDs into an existing protocol for the treatment of chronic pain is relatively straightforward, given the shared focus of both interventions on identifying maladaptive cognitions, decreasing the use of avoidance to cope with problems and increasing engagement in appropriate activities.

Evidence for the efficacy of Cognitive Behavioral Therapy for pain

Psychological interventions have demonstrated efficacy for reducing pain and improving functioning in persons with a broad spectrum of pain-related conditions [49-51]. However, this form of treatment has not been well-tested in those with SUDs. Given the complicated and multidirectional relationship between pain and substance use in SUD patients [52], it is unknown whether the well-established effects of CBT for pain[50] will apply to this patient population.

For other patient populations, psychological interventions are associated with lower post-treatment pain and better functioning than either wait list controls or other active control conditions[23, 51]. A comprehensive meta-analysis of 25 trials indicates that CBT for pain produced significant reductions in pain and negative affect compared to wait list and attention control conditions[50]. CBT interventions were associated with a moderate effect size (of .5) despite a high degree of variability in the quality of trials and types of pain studied. Many of these studies have strictly adhered to the CONSORT guidelines [53] and provide a strong test of the efficacy of the intervention. However, an unfortunate consequence of the methodological rigor of this prior work is the frequent utilization of strict subject exclusion criteria; most prior trials of CBT for pain have excluded patients with co-occurring SUDs, and the applicability of the established effects to those with drug or alcohol problems is mostly unknown. To the best of our knowledge, only two published studies have explicitly examined the effects of CBT for pain in those with SUDs [45, 54]. Currie et al. [54] examined 44 patients in Canada with both SUDs and chronic pain and found significant reductions in pain, pain-related interference, medication misuse and more general measures of maladaptive coping from baseline to 12-month follow-up. Our group recently found that pain levels and alcohol-related problems decreased, and pain management self-efficacy increased following the delivery of CBT for pain and SUDs in an addictions treatment program[45]. However, both prior studies lack control groups and better data are needed to more firmly establish the impact of CBT for pain and SUDs on long-term treatment outcomes.

Gender and pain management in SUD patients

Existing evidence indicates that pain is at least as common if not more so in women as men entering SUD treatment [17-21]. However, prior research has lacked sufficient numbers of women to examine gender differences in the characteristics of men and women with pain in SUD treatment. Additionally, a number of differences have been reported between men and women in non-SUD-related research in terms of the frequency, intensity and duration of pain [55]. Emerging research suggests that men and women may differ in their response to the analgesic effects of pain medications [56-60]. Similarly, a few studies indicate that psychosocial interventions for pain may differ in terms of their magnitude or mechanism of effect depending on gender [61-63]. Moreover, although research on gender differences in research on pain has increased dramatically over the past 20 years [55], most studies of psychosocial interventions for pain have lacked sufficient power to examine gender differences. Given these conflicting findings, it would be premature to design and fully power a study around a specific hypothesis related to gender as a potential moderator of the effects of psychosocial pain interventions. However, it is essential for newer research to be fully powered to detect the effects of pain-related interventions in both men and women.

Opioid pain medication misuse

Rates of prescribing and misuse of opioid pain medication have increased significantly since the mid 1990's in the United States [31]. Additionally, the frequency of adverse events linked to prescription pain medication misuse such as non-fatal [64] and fatal overdoses [65] have increased rapidly. While the rate of misuse of prescription pain medications has increased, the development of efficacious treatment methods for treating abuse or dependence on pain medications has not kept pace. On one hand, it is possible that individuals who misuse pain medications may respond sufficiently to standard SUD treatment. However, it is also possible that standard SUD treatment paradigms will produce less than optimal results in these patients. The latter possibility is more probable in those with persistent pain and for those who have problems with opioid medications as well as other substances. Despite the fact that rising rates of misuse of pain medications has increased concern about the relationship between pain and other substance misuse, it is important to note that most patients with pain in SUD treatment programs have patterns of substance misuse that are not limited to opioid medications. Thus, a more comprehensive approach to the treatment of pain during SUD treatment should address the co-occurring pain and SUDs and include both those with and without current pain medication misuse.

Pain, HIV risk behaviors and depression

On average, SUD patients with pain report greater functional disability relative to other SUD patients without pain. Although a psychosocial intervention targeting pain and substance misuse would primarily address these outcomes, it is possible that receipt of this intervention would also lead to improvements in other domains such as HIV risk behaviors and *depression*. In particular, it is possible that combined CBT for pain and SUDs could have broader benefits for reducing HIV risk behaviors irrespective of initial HIV status. This is likely to be particularly true if risky substance use has been used previously as a method for coping with pain. In addition, prior research has consistently demonstrated the high rates of pain (often greater than 60%) in those with HIV/AIDS [66]. Preliminary evidence also indicates that CBT may successfully decrease pain in those with HIV [67, 68]. *Similarly, depressive symptoms are consistently linked to pain [7, 20, 69, 70] and prior evidence in those without SUDs indicates that depressive symptoms improve following psychosocial interventions for pain [71]. Given the important societal implications of addressing both HIV risk behaviors and depressive symptoms in those with chronic pain and SUDs, it is important to examine whether a psychosocial intervention addressing pain and substance misuse also leads to changes in these other crucial domains.*

Summary of literature

Despite the large numbers of patients in SUD treatment who report significant pain, treatment providers lack clear guidelines or evidence-based treatments for how to treat pain in these individuals. Additionally, pain predicts poorer post-treatment drug- and alcohol-related outcomes in those treated for SUDs [17]. Treatment providers in SUD programs need alternative strategies to manage pain in these patients. Cognitive behavioral treatment for pain represents a promising treatment option but the impact of this strategy in drug and alcohol patients has not been closely examined. More broadly, examinations of interventions for pain should be powered to detect effects in both men and women [55]. The proposed project is designed to test the effect of a CBT intervention for men and women with chronic pain who are already engaged in residential treatment for substance use disorders compared to a Supportive Psychoeducation Control (SPC) condition on pain-related measures (pain intensity, pain-related disability and pain tolerance) and substance use (frequency of illicit drug and alcohol use and extent of opioid medication misuse).

Preliminary Studies

The proposed study builds on the project team's substantial prior experience in studying the association between pain and SUDs. Within this section, we describe our prior experience: (1) examining the prevalence and associated complications of pain in SUD patients, (2) conducting randomized controlled trials of behavioral interventions related to other co-occurring problems in SUD patients, (3) gathering behavioral measures of pain tolerance, (4) evaluating a similar intervention in a group with high prevalence of SUDs (i.e., patients with HIV), and (5) collecting pilot feasibility data on the intervention in the study site. This work has resulted in the creation of detailed manuals for both the CBT and Supportive Psychoeducation Control conditions which are included in the Appendix.

Prevalence and associated problems of pain in SUD patients. Our early analyses of patients in opiate substitution treatment programs indicated that over half of all patients in this sample (52%; n=130/251)

reported significant pain at baseline [16, 33]. Patients with significant pain at baseline reported greater illicit use of opioid and sedative medications and cannabis than patients without pain. Patients with pain at baseline continued to have more severe problems in other domains of functioning, such as mental health, at 1-year follow-up. Although the proposed study focuses on pain in more general samples of those with SUDs, this initial work highlighted the high prevalence of pain in SUD treatment settings and the clear need for improved interventions with these patients.

Prior experience with SUDs, including developing, refining and testing behavioral interventions. Members of our research team (Drs. Blow, Barry and Chermack) have a long history of NIAAA/NIDA funded research developing and delivering interventions to those with SUDs, and also have extensive experience conducting research with SUD treatment samples [72-78]. The prior and ongoing work of the research team has been conducted in several different types of care settings (primary care, emergency department, SUD treatment settings), addressed a wide range of age groups (adolescents through older adults), a range of target behaviors (alcohol/drug use, treatment engagement, interpersonal violence), have generally involved interventions integrating CBT approaches with other treatments (e.g., adaptations of motivational interviewing), and have typically had follow-up assessment rates ranging from 85%-90%. Drs. Chermack, Barry and Blow also recently completed a NIDA-funded behavioral therapy development grant focused on violence prevention for men and women in substance abuse treatment that was partially **conducted at the proposed study site** [79]. Additionally, Drs. Ilgen, Chermack and Blow are currently conducting a NIDA-funded R21 of a suicide-reduction intervention **at the proposed study site**. Importantly, these studies began a period of collaboration between the investigative team and the study site, Community Programs Inc., in Waterford, MI.

Experience gathering behavioral and self-report data related to pain. A unique strength of our research team is our high degree of experience with measures of pain and pain tolerance. Drs. Trafton (consultant) and Ilgen have experience collecting preliminary data on pain tolerance using the cold-pressor task in methadone maintenance patients. As part of a recent pilot study, 41 opioid-dependent methadone maintenance patients were administered the cold-pressor task. An initial manuscript based on this study emphasized the impact of stress on craving for substances [80]. The experience gained from this study confirmed the utility of behavioral measures of pain tolerance in SUD patients and helped to influence the current focus of our intervention on increasing pain tolerance as well as the traditional outcomes of pain level and pain-related functioning.

CBT for pain in patients with HIV/AIDS. The current CBT intervention developed out of a series of pilot studies that began with Dr. Trafton's work in patients with HIV/AIDS – many of whom had extensive illicit drug use. Cucciare and colleagues [67] describe a preliminary evaluation of this intervention in 70 participants. In this initial sample, 81% of patients had an SUD. In terms of the response to the intervention, 86% of patients reported being highly satisfied with the therapy, and despite reporting numerous logistical barriers to regularly attending in-clinic sessions, patients attended a mean of 4.29 ± 4.2 group sessions. Study participation was associated with improvements in pain severity and overall pain-related impairment.

In the 12% of patients who were using substances at baseline, there was a trend towards reduced substance use over the 12 weeks of treatment (days of use in the last 30: baseline: 7.8 ± 8.5, 12 weeks: 2.6 ± 3.2, p=.11). We were clearly underpowered to detect all but the most robust effects within this small subset of participants but these findings provided an early foundation for our later work.

Preliminary data on the potential impact of the CBT intervention in SUD patients. In order to obtain preliminary data on the proposed intervention, we have collected data on pre- and post-treatment functioning in 26 patients. These studies were conducted in two clinical settings: an outpatient VA SUD clinic (see Ilgen et al.[45]) and a residential SUD program (CPI, the study site). Despite the small number of participants, we found that pain reduced significantly [from an average of 6.4 (± 2.1) to 5.3 (± 2.2), $p < .05$] from pre- to post-treatment. Also, consistent with the theoretical basis of the intervention, self-efficacy to manage their pain without misusing drugs or alcohol increased significantly [from 146.2 (± 49.9) to 188.3 (± 50.8), $p < .01$].

Although we did not collect data on post-intervention substance use in participants recruited at CPI, in the VA outpatient SUD sample, we found that ASI alcohol composite scores improved significantly during the course of the group. Drug composite scores did not change substantially from pre- to post-treatment; however, these findings likely reflect a floor effect given the low levels of baseline pre-treatment drug use in the VA outpatient SUD clinic.

Overall, the intervention group appeared to be well-tolerated and rates of treatment attendance were high. Over 87% of individuals who initially consented to this project completed at least four sessions of the CBT group. These numbers demonstrate a high interest and desire of the participants to improve upon their chronic

pain and substance use experiences. Qualitative data collected at the conclusion of the intervention also indicate that participants were very positive about their experiences in the intervention.

Feasibility of screening and recruitment at the study site. In order to conduct the pilot study and to refine our recruitment procedures at the study site, we screened 94 CPI patients for their levels of pain and pain medication misuse. This pilot work also allowed us to refine a method for initially screening and managing data collection at CPI. We have designed a screening process that involves announcing the potential to participate in the research project during the daily meeting for all patients. Participants are encouraged show up and/or sign up to complete the screening which may be conducted throughout the day in a smaller room on site. Although participants have several hours of treatment programming each day, they also have periods of free time that allows them to be available for participation in the research if they are eligible and interested. This process has allowed us to successfully screen large numbers of participants without interfering with ongoing treatment at the facility.

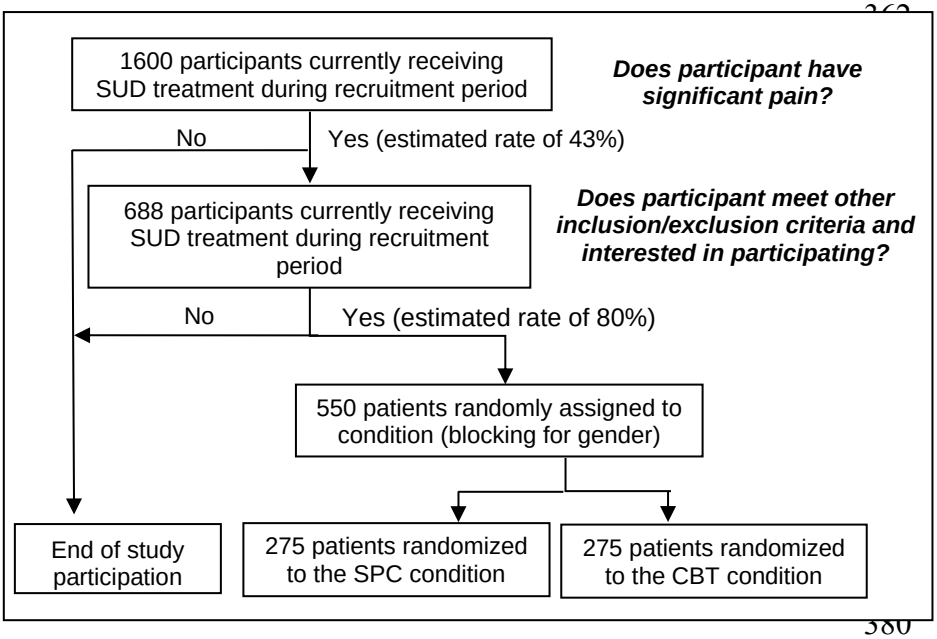
The data collected thus far indicate that, on average, the men at CPI were 36.9 years old and women were 33.9 years old. In terms of racial background, men at CPI were: Caucasian (56%), African American (35%), or other (9%). Women were: Caucasian (80%), African American (16%), or other (4%). During the screening process, over 53% of participants reported pain of at least 5 or greater on the Numeric Pain Rating Scale. Of these individuals, 85% reported at least some misuse of pain medications in the past 30 days.

Upcoming study of CBT for pain in VA outpatient clinic. Recently, we received funding for a 3.5-year study of CBT for pain in Veterans seen in an outpatient VA SUD clinic. Participant recruitment began June 15, 2010. Conducting this study in the VA will further refine many of the components for the proposed study (measures of fidelity, control condition manual, etc.) and will facilitate delivery of all aspects of the proposed study. The proposed study extends our work in this area in new directions. First, based on our knowledge of the two SUD programs and our pilot data, it is clear that, relative to the VA study, the proposed study sample will be younger and more ethnically/racially diverse, with poorer contact with primary care providers and higher severity of social impairment. Second, men make up over 90% of all patients in the VA study. The proposed study will provide one of the first opportunities to separately study outcomes of the intervention for men and for women, and will lead to new approaches across genders. Finally, Drug Use Disorders are highly prevalent at the proposed study site. Our VA-based work has dealt more with alcohol problems and pain. This proposed study will provide new knowledge to the field in the area of all drug use disorders and pain. This proposed study places an emphasis on the extent to which the CBT intervention (vs. SPC) improves post-treatment substance-related outcomes, a new area of research.

IV. Research Design and Methods

The proposed study is a randomized trial of two conditions: group-based CBT or Supportive Psychoeducation Control (SPC) condition delivered to patients already receiving residential SUD treatments. We anticipate screening 1,600 participants. .

Figure 2. Study design.



We use a conservative estimate that up to 550 of those individuals with significant chronic pain will meet other inclusion/exclusion criteria and consent to participate in the trial. Participants will be up to 550 persons (approximately 275 men and 275 women) with chronic pain (inclusion and exclusion criteria listed below) recruited from a residential SUD treatment site, randomly assigned in groups of approximately 8 to 12 participants to one of the two conditions (as described below) and assessed at five time points [baseline, 1 month post-baseline (also referred to as end-of-intervention), 3, 6 and 12 months after intervention completion]. Data on current patients in the proposed study site indicate that CPI provides non-detoxification residential services for over 630 unique individuals (~420 men and ~210 women) each year. Non-Caucasians make up approximately 44% of men and 20% of women who receive residential services at CPI. Minority patients will be encouraged to participate during recruitment.

Participants

Participant recruitment. Potential participants will be patients with chronic, moderate to severe pain currently receiving SUD treatment services. Study personnel will describe the study during the large daily meetings at the study site and invite participants to sign up to be screened in a separate room at the facility. Participants will be consented and screened in smaller groups and, if eligible, scheduled for the baseline assessment. The project coordinator and/or research associate for the study will conduct the initial screening, initiate the process of obtaining written informed consent, and then conduct the baseline assessment. This is the process of recruitment that we developed and refined during pilot data collection and allowed for the screening of large numbers of potentially eligible patients. When using two study staff, we found that we could screen anywhere from 30-50 participants in a single day and conduct the more detailed baseline assessments of eligible participants within the next 2-3 days.

Inclusion/Exclusion Criteria

Data will be collected from men and women aged 18 and over enrolled in an SUD treatment program at the study site(s). Based on the responses to the screening instrument, participants may be eligible to participate in the larger baseline assessment if they:

The *inclusion criteria* are: 1) a report of pain of at least moderate or greater intensity over the three months prior to baseline assessment as indicated by an average score of five or greater on the Numeric Rating Scale of pain intensity (NRS-I [81]); and 2) completion of an intake assessment at the SUD program within the 60 days prior to baseline assessment (which will leave sufficient time for participants to participate in the intervention prior to discharge from their treatment agency). The pain-related inclusion criterion will be used to ensure that participants are experiencing elevated levels of pain and, consequently, are appropriate for pain-related treatment. If participating in Part II of the study, participants should anticipate being at the treatment site long enough for the duration of intervention.

The *exclusion criteria* are: 1) acute suicidality based on responses on the Beck Depression Inventory confirmed by in-depth assessment of patient by the research associate; 2) psychiatric condition that precludes participation in the intervention based on *(a)* a Mini-Mental State Examination (MMSE) [82] score of less than 21, or *(b)* endorsement of current psychotic symptoms on the Brief Symptom Inventory (BSI) [83], and/or noticeable bizarre thoughts or behavior during the interview; 3) inability to speak and understand English; and 4) inability

to give informed, voluntary, written consent. Decisions about exclusion criteria 1 and 2 will be made using a combination of self-reported symptoms and researcher's judgment in consultation with clinician investigators. Patients may be excluded from participation if they have been in treatment at the study site for more than 60 days..hese exclusion criteria were chosen in order to exclude participants in need of more immediate and intensive psychiatric treatment. Intensive psychiatric services are not available at the study site and acute treatment typically involves receiving services at an outside location. Due to the sensitive nature of this study, the PI will have final discretion in the inclusion/exclusion of participants. Additionally, these criteria ensure that participating patients will be capable of benefiting from a group intervention and not be disruptive in the group.

Procedure

Overview of recruitment and intervention delivery. Study recruitment and delivery of the intervention may occur in ***six-week blocks at both the men's and women's*** *residential treatment units. The initial screening and assessment process will take up to one week (i.e., week 1 of each six week block). Following the assessments and consent, participants will be randomized in groups of anywhere from about 8-12 participants (depending on the number of participants recruited) to either the CBT or SPC condition. Typically, at any given time, only one group will be conducted at either the men's or women's unit (so, typically 2 groups running simultaneously but on different units). If necessary and plausible, we may run additional groups. The groups will last for about 4 weeks (i.e., weeks 2-5 of each six week block) and both the CBT and SPC groups will be "closed" (i.e., only accept participants around the start of the group). AMEND 24386-Please note, although we anticipate running each group 2 times a week for 4 weeks, given scheduling issues (ex. vacations, study sight space issues, holidays, unforeseen circumstances), we will schedule the group accordingly (ex. run a group 3 times in one week, run the group for 4.5 weeks). Participants will be informed by the therapists and/or study staff of any such changes. Additionally, although we will use this recruitment strategy as a guide, we may find that we can vary the time it may take to recruit participants and will adjust our recruiting strategy (ex. recruit within a 4-week block) and group commencement accordingly. These changes will not affect the fidelity of the data collected in the study.*

Post-treatment assessments will be carried out during the following week (ex. week 6 of the six-week block), and the process will repeat itself the following week. In any given year, we anticipate that we will conduct approximately eight, 6-week blocks (52 weeks in a year, minus 2 weeks for vacations in late December, divided by 6 equals 8.33). AMEND 24386- Please note that baseline and follow-up assessments may be adjusted according to the group beginning and end dates.

If approximately 20 participants (10 men and 10 women) are recruited during each of these six-week blocks per year (or 160 participants per year), it will take approximately 3 years (3 X 160 = 480) to recruit the 550 participants for the RCT portion of the study. We have slightly overestimated the amount of time (by a little over 6 weeks) in order to allow for any unanticipated delays. The study timeline is depicted in the Gantt chart in the Appendix.

Informed consent. Written informed consent will be obtained from all participants. Separate consent will be obtained for the screening and RCT portions of the study. The proposed study team will apply for approval from the University of Michigan's Institutional Review Board and will also apply for a Certificate of Confidentiality from the National Institute on Drug Abuse (NIDA).

Randomization procedure. Following completion of the baseline assessment and consent, each group of about 8 to 12 participants will be randomly assigned to: 1) group-based CBT; or 2) the SPC group. *We will stratify the randomization by gender (male/female). We considered balancing the treatment groups further by pain severity and prescription pain medication use, but further stratification would make the study logistically difficult to carry out We will, however, evaluate baseline balances in pain severity after 10 groups have been randomized, and if balancing with respect to pain severity or pain med use appears to be of concern, we will have a better understanding of covariate distribution at that time to adapt randomization based on covariate values where we will potentially select a group (cluster) by randomly selecting preset proportions of patients within covariate strata. Unlike the adaptive design modifying sample size estimation, this adaptive design, if applied, will not require adjustment of type I error* [84]*.*

Study site and recruitment feasibility. This study will be conducted at a residential SUD treatment center, Community Programs, Inc. (CPI), in Waterford, Michigan, where we have successfully conducted several of

our prior studies. This treatment site was chosen because it serves a large heterogeneous population of men and women with SUD problems and has a long-standing positive relationship with the study team. Established in 1968, CPI is one of the largest treatment centers serving the metropolitan areas of Flint, and Detroit, MI and the surrounding areas. CPI provides separate residential services to approximately 420 men and 210 women each year. Under usual care conditions, participants stay in the residential treatment facility for 60 days and approximately 77% complete their intended course of residential treatment. CPI will provide office/group rooms on an as-needed basis for conducting private research interviews and therapy sessions (see letter of support in Appendix). The combination of the large volume of patients with a supportive staff that has collaborated previously with our research group makes CPI an ideal setting to conduct the study.

Our pilot screening data indicate that approximately 50% of CPI patients have moderate or greater pain and would meet other study inclusion/exclusion criteria. Although we based our estimates on the rates of eligible participants on our pilot work, we anticipate that we would have no difficulty recruiting sufficient numbers of participants even if the rate is significantly lower during certain periods of recruitment. For example, even if rates of pain dropped to 40% of CPI residents, with the high number of participants (estimated at well over 1,850 unique participants over the 3-year recruitment period), we would still be able to easily recruit the target sample of 275 participants per gender for the study. Specifically, even in the worst case scenario, for women participants, we expect to have 252 eligible participants in 3 years (210 X 3 years X 0.4 with pain).

Participant retention, differential dropout and follow-up. Participants will be remunerated $5 for participation in the screening. All remuneration for the study will be in the form of gift cards, cash, or amount placed into the participant's account at the agency (ex. CPI). Participants who consent to the RCT portion of the study (AMEN 24386, updated AMEN 27764) will be given $20 for completing the baseline assessment (i.e. initial enrollment) and an additional $5 for voluntarily providing a urine sample. Subjects will be given $25 after completing the first (approximately 1-week after the therapy group is complete) follow-up assessment plus an additional $5 for a voluntary urine sample; $30 for completing each of the 3 and 6 month follow-up assessments plus an additional $5 for each voluntary urine sample at these assessments; and $35 dollar for completing the 12-month follow-up assessment plus an additional $5 for a voluntary urine sample. Subjects can receive an additional $5 per follow-up for contacting research staff within two weeks of their 3-month, 6-month, or 12-month assessments. This strategy will not be used at the 1-month follow-up because participants will still be in the residential treatment program. Instead, participants may be eligible to earn $5 for updating their contact information after (or around the time of) discharging from the study site (i.e., CPI).These participants' payments are not contingent upon treatment participation.

At the 3-, 6- and 12-month post-treatment follow-ups, we will use a series of strategies to locate participants that have been used successfully in our previous research. Previously, in our pilot feasibility trial at this study site, we obtained post-treatment follow-up data from 87% of participants who began the group. In other studies with longer-term follow-ups, our research group has developed a variety of successful strategies to increase follow-up rates including asking participants to designate at least two contact persons who will be aware of their whereabouts should they become unreachable, providing participants with multiple reminder phone calls before appointments, and encouraging continuity of contact with individuals on the research team. Finally, we will use an analytic approach that minimizes the impact of missing data on estimation of outcomes.

Follow-up assessments will be conducted in person whenever possible to allow for the collection of urine drug screens and measures of pain tolerance. The research staff member will contact participants and ask them to come to the study office at the study site or arrange to meet them at a convenient location (e.g., their home, library, restaurant, etc.). If we interview participants in their homes, we will typically arrange for an escort to go with the research staff member for staff safety reasons and/or a phone-in system with study staff. As a part of our recruitment and throughout the study, small items of insignificant value (i.e. pop, water, water bottles, card holders, pens, stickers, etc.) may be utilized (e.g.in group, if meeting in public) and will not be used as a contingency of study participation. Participants who move out-of-area will be interviewed by phone at follow-up; in our experience this will be <10% of participants from this SUD treatment program. Additionally, surveys may be sent via mail to the participant (e.g. in cases in which an in-person assessment is not possible). Participants that mail their survey will be asked to return it without any identifying information (i.e. name, telephone number) on the survey(s) or returned envelope. When possible, a self-addressed stamped envelope to the study staff member (i.e. research coordinator) will be provided. Additionally, to help retain participants, we may mail or give in-person appointment reminder cards and/or letters. Samples of these letters

and reminder cards have been uploaded to the IRB application.
Amen 27764-We have set up an email account to be used for subjects to contact study staff or for study staff to send appointment reminders to subjects. The e-mail address is: starstudy@umich.edu. Through the study email account, we have also set up a Facebook limited profile page. The Facebook profile page lists only the study name, contact information, and affiliation with UM. Facebook will NOT be used as a recruitment tool. The account is set up as a source for private messaging between study staff and enrolled subjects. The message shows up in the person's private inbox, similar to an e-mail message. There is no ability for an individual to send a "friend" request to the study or post on the study wall. Only subjects with active Facebook accounts can be messaged. Privacy settings are checked regularly (ex. on a weekly or monthly basis).The Facebook page can be found at: . https://www.facebook.com/star.study Participants will also be able to contact study staff or correspond/receive appointment reminders through text. When providing contact information, the subject will indicate if study staff can contact them through text, email and/or Facebook.

AMEN 27764- Subjects may be sent greeting cards on holidays and birthdays in an effort to retain participants. Subjects may also receive a certificate of recognition at the end of their therapy group and/or at the end of the study. The certificate will congratulate the participant (include their name) for completing the appropriate part of the study. We may also include a business card for official study use, such as when meeting or sending correspondence to participants. A study official business card may include affiliation to the University of Michigan, study name, and contact information. Individual study staff names may also be included.

Treatment conditions

Cognitive Behavior Therapy (CBT). CBT will be provided by one of two master's-level therapists with expertise in this approach. Therapists will follow the manualized treatment protocol previously developed by Drs. Ilgen, Chermack and Trafton (see Appendix). Participants receiving the CBT pain management intervention will also attend their standard treatment protocol at their treatment agency.

Because we will use a cohort admission design, participants will attend the first session of the group (typically up to 8 days) after completing the baseline assessment. AMEN 24386-In the case in which a participant has completed a baseline assessment, but that the group is "full", the participant may be offered the opportunity to attend the next round of groups. This cohort approach is often used in the study of CBT for pain [42] and will allow for the examination of specific "group" effects in our analyses. Each group will contain anywhere from about 8-12 participants.

Typically,treatment will consist of approximately eight, 1-hour structured sessions provided two times each week over the course of 4 weeks. The 4-week closed-group format allows for a standardized progression with content built upon the previously presented treatment materials. The protocol includes an introduction session consisting of education on a psychosocial model of pain, and a final session consisting of a review of pain management skills as well as relapse prevention. Each session will begin with a brief check-in of homework, review of the psychosocial model of pain, and an outline of how the specific topic for the day (e.g., behavioral activation) relates to the overall psychosocial model of pain. No single session will be focused exclusively on substance use. Instead, content related to substance use will be integrated into each session's specific pain-related focus. Substance use will be primarily conceptualized as a maladaptive coping response and the treatment will address substance use by increasing the use of more appropriate coping skills and improving self-efficacy to manage pain without substance use. Based on our experiences in the pilot study, we modified the intervention content to be appropriate for participants in residential treatment and, consequently, in a controlled environment. Participants in the intervention condition will receive a copy of the manual.

In terms of specific content areas, the concept of acceptance is an overarching theme that will be emphasized across all sessions. This approach generally highlights the importance of identifying specific goals for better functioning and working towards these goals during treatment. Additionally, two sessions are focused primarily on acceptance, including handouts and discussion of the willingness to acknowledge harmful coping versus healthy coping and nonjudgmental description of emotions, thoughts, and situation that influence the ability to implement healthy coping skills. *All sessions highlight the importance of tolerating depression and anxiety and sessions 3 and 6 specifically focuses on addressing depression and anxiety.* The aspect of treatment focused on cognitions includes sessions on thought monitoring, cognitive reconceptualization and cognitive restructuring. The behaviorally-oriented content includes sessions on behavioral activation and attention diversion. Pacing [85], or strategically planning to avoid over-activity, is another behaviorally-oriented

theme that will be reiterated throughout the 4 weeks. *Behavioral activation is also used as a method to address pain and decrease depression. Participants may also* practice a relaxation exercise that ranges in length from 5 to 15 minutes during these sessions. Throughout the group, we will emphasize the importance of understanding the ways in which using illicit drugs or alcohol or misusing pain medication may interfere with other, more appropriate methods for managing pain. Although obtaining opioid pain medications is difficult on a residential unit, some participants may receive ongoing or occasional pain medications from their medical staff while in treatment. Participants will not be required to remain abstinent from all pain medications during the group; instead, treatment will focus on steps to avoid misuse of opioid medications after completion of the residential treatment episode.

Supportive Psychoeducation Control (SPC). We designed this group to match the CBT condition in terms of level of attention and the non-specific aspects of receiving support for pain and substance misuse. Specific content related to pain for the SPC group is similar to that which was used by Turner, Mancl and Aaron [71], modified to cover multiple pain conditions; content related to substance use will based on psychoeducational attention control treatment for alcoholism (PACT) [86], modified to cover other substances in addition to alcohol. Patients participating in this group will receive a revised copy (ex. therapist notes deleted from the therapist version) of the manual and the sessions will be based on chapters from this manual. The sessions will help patients to better understand the origins and consequences of pain and substance use in their life. However, topics related to psychological factors associated with pain and possible psychosocial coping mechanisms will not be a part of the formal content of the group. Thus, the group will not directly overlap with the content of the CBT group.

Treatment as Usual at Community Programs, Inc (CPI). Both the CBT and SPC conditions will be overlaid onto a standard episode of residential treatment at CPI. Residential treatment at CPI involves a combination of relapse prevention and 12-step principles to encourage abstinence and improve coping skills. Treatment typically involves therapist-led treatment groups, peer-based self-help groups, and daily responsibilities related to the functioning of the residential unit. These aspects of treatment are typically provided between 5-7 hours per day and are mostly consistent across participants. For those with co-occurring psychiatric or medical problems, supplementary psychiatric medication management and medical care are available. No efforts will be made to influence the prescribing practices of other providers and study therapists will be barred from discussing clinical information about participants with CPI staff, except in cases in which reporting (ex. suicide, homicide, child abuse) is clinically necessary. Concurrent pain medication use may be measured via self-report and/or medical chart review.

Treatment contamination during the study. Because patients assigned to both conditions are being treated at the same residential SUD facility, it is possible that they will talk to one another and discuss their experiences in treatment. To diminish risk of contamination between conditions, typically, we will stagger delivery of the conditions on the men's and women's units (with a new treatment group delivered about every six weeks) so that two groups will not occur simultaneously. However, given that the average length of stay is 60 days, participants in one group will still be at their treatment agency when the second group begins. It is worth noting that the treatment site is extremely large and participants in either condition (about 8-12 at any given time) will be a small minority of the total number of participants in the residential facility. This decreases the chances that significant contamination will take place. Nevertheless, conducting the study at a single residential facility raises three possibilities related to contamination: (1) c*ontamination of CBT with elements of the SPC (control) condition*. The SPC condition will present information on the physiology for pain and on the consequences of drug/alcohol use that is widely available in the community (i.e. pharmacy pamphlets, etc.). Thus, the discussion of this information by SPC members with CBT members should not "contaminate" the CBT condition with any information that would not normally be discussed in response to standard patient questions about pain or that is substantially different from what is often discussed in standard SUD treatment. Perhaps of greater concern is the possibility of (2) *contamination of the SPC condition with elements of the CBT treatment*. If any contamination does occur, it is expected to be minimal. CBT will be delivered by trained therapists in a systematized manner. Informal interaction among patients is unlikely to provide therapeutic benefits commensurate with participation in the group. However, we will be assessing the presence of key components of the CBT intervention (self-efficacy, motivation, coping and acceptance) in all patients so that

we would be able to detect if SPC participants report significant increases in these domains during the follow-up time period. Additionally, we will be monitoring the content of both groups and coding for fidelity to both the CBT and SPC conditions. If participants in the SPC group are exposed to content from the CBT group and discuss this in the SPC group, this will be detected as part of the ongoing measurement of integrity of the SPC condition. (3) *Contamination of standard treatment at the study site with elements of either of the two conditions.* Both conditions will be provided by members of the research team not affiliated with the study site. Thus, the intervention providers as part of this project will not directly influence the standard course of SUD treatment in these patients. Neither of the two treatments makes explicit or implicit recommendations about how the patients should change their overall approach to treatment course (i.e., length of stay, medication doses, etc.) at their agency. The study site is a large and multifaceted residential site. In our prior experience, we have found that, although they are very welcoming of the research team, the staff at the study site are very busy and standard of care is not directly impacted by our presence.

It may occur that participants may miss sessions or need to make up a session. Missed appointments or treatment sessions may be rescheduled, as needed, in a timely fashion in order to maintain data integrity (for example, may occur slightly outside the 4 week treatment period).

Study Fidelity Monitoring

Therapist monitoring and treatment integrity. The successful delivery and integrity of treatment will be established and assessed through both direct and indirect methods. We will employ treatment manuals for the delivery of the CBT and SPC groups. Mastery of the treatment manual will be demonstrated by satisfactory completion of a written test of the information contained in the manual. During the first six months of funding, we will finalize measures of adherence and competence that meaningfully distinguish between the CBT and SPC conditions. Specifically, we will modify the CBT portion of the Yale Adherence and Competence Scale (YACS) [87] to include specific content from our treatment manual to allow for third-party ratings of the content of treatment. All group sessions of the CBT and SPC groups will be audiotaped, and 25% of tapes will be randomly selected to be transcribed and assessed by the research associate (s) and/or project coordinator to ensure that key aspects of the manualized treatments are presented in the sessions. These transcribed tapes will be doubly coded by the two raters and inter-rater agreement will be calculated. Detailed criteria for the raters will be based on the YACS. Percentages of treatment integrity/violations will be calculated. Additionally, Drs. Ilgen and Chermack will listen to 25% of all audiotapes and provide corrective feedback to the therapists whenever drift occurs. Ratings of treatment integrity/violations will be specifically monitored for differences among therapists and evidence of drift or treatment integrity violations will be specifically addressed.

Intervention receipt will be established through various methods. Receipt of CBT- and SPC-related information will be assessed with short self-report measures that are analogous to a manipulation check at the last session (can be made up during first assessment, if necessary). Any incorrect answers will be discussed in the group and misunderstandings will be clarified. These questions will be drafted during the first six months of the project. *Additionally, to inform future work examining potential mechanisms of action, participants will be asked during the last session of both the CBT and SPC groups to identify the content of the groups that they found to be most helpful.*

Study Assessments

Study assessments. Participants will be assessed on the following schedule. First, they will be screened briefly for eligibility. Next, all eligible participants will complete the full research assessment at baseline, and follow-up assessments at the end of the intervention, and at three, six and twelve months after the intervention (i.e., months 4, 7, and 13 post-baseline). Whenever possible, the research staff member conducting the assessment will remain blind to participants' treatment assignment, however, due to staffing/budget issues, we may find this is not possible. Assessments of perceived treatment credibility and comprehension of materials (described above) will be administered by the study therapist during each session. (AMEN 24386)-Please note, we may find it necessary to delete questions due to issues such as time considerations and to lessen the participants' burden, Additionally, surveys mentioning time periods (i.e. last 30 days, "since the last time I saw you") may be updated to the appropriate time period (i.e. last 3 months, last three months prior to entering a controlled environment, three months excluding being in a controlled environment such as jail, etc.) depending on the assessment (ex. 1 month vs. 12-month assessment). Because participants may be confused by certain

substances on our questionnaires (ex. cannabis), we may also include (an) alternative name(s) for the substance (ex. marijuana). These changes will not affect the fidelity of the data collected in the study.

Screening. The screening assessment will include questions about current level of pain and length of participation in SUD treatment. Participants will be asked about their pain level using the Numeric Rating Scale of pain intensity (NRS-I) [81] an 11-point numeric rating scale (0 = no pain, 10 = worst pain imaginable). Participants will be asked to rate their usual and worst pain over the past 3 months. We will use an average of these two ratings of 5 or greater on the NRS-I as one of our primary eligibility criteria. Initial information on the participants' race, ethnicity and gender will be collected during the screening. Participants will also complete measures of psychological distress and depression (BSI and BDI-II). Additionally, participants will be asked how long ago they completed their intake assessment at their treatment agency.

Full research assessment. The following section outlines the sources and content of research data that will be collected over the course of this study. These assessments will cover five broad domains: 1) demographic information, 2) pain, 3) mental health and functioning, 4) substance use and 5) treatment experiences, potential mechanisms of action and secondary outcomes. *Participants will also report the number of days they spent in a controlled environment since the last assessment as part of the Time Line Follow Back (TLFB* **[88])**.

Overview of assessments. Most assessments will be self-report and are listed below (with corresponding citations). Appendix provides more detailed information about the development and psychometric properties of the self-report measures. Additionally, we provide further info in the text following Table 1 on measures of pain tolerance and the urine drug screens.

Table 1. Schedule and content of study assessments to be completed by participants.

Assessment Instruments (Construct)	**Screening 20 minutes**	**Base-line**	**After each session**	**Post-intervention (1-month)**	**3-month* follow-up**	**6-month* follow-up**	**12-month* follow-up**
Demographics	X						
MMSE [82]		X					
NRS-I [81]	X			X	X	X	X
BSI [83]	X			X	X	X	X
BDI-II [89]	X			X	X	X	X
Overdose	X						X
Legal Status Questionnaire	X						
Medical Marijuana Questionnaire	X						
PHQ-9 [90]		X		X	X	X	X
SF-12 [91]		X		X	X	X	X
PANAS		X		X	X	X	X
CSQ		X		X	X	X	X
MBM		X		X	X	X	X
ASSIST		X		X	X	X	X
STAI [92]		X		X	X	X	X
SF-MPQ-2 [93]		X		X	X	X	X
WHYMPI [94]		X		X	X	X	X
Ischemic Pain Task		X		X	X	X	X
TLFB [88]		X		X	X	X	X
COMM [97]	X			X	X	X	X
SAOM [98]		X		X	X	X	X
Urine Drug Screen		X		X	X	X	X

HRBS[99]	X			X	X	X	X
CPSS [101]		X		X	X	X	X
CPCI [103]		X		X	X	X	X
CPAQ [104, 105]		X		X	X	X	X
SMQ	X						
ASI	X						
PMEQ		X		X	X	X	X
Session Attendance			X				
Treatment Satisfaction /(WAI)**				X			
Treatment for Pain	X						X
YACS [87]			X	X			

ASI=Addiction Severity Index; ASSIST=Alcohol, Smoking, and Substance Involvement Screening Test; BSI=Brief Symptom Inventory; BDI-II=Beck Depression Inventory-II; COMM=Current Opioid Misuse Measure; CPAQ=Chronic Pain Acceptance Questionnaire; CPCI=Chronic Pain Coping Inventory; CPSS=Chronic Pain Self-Efficacy Scale; CSQ=Coping Strategies Questionnaire; HRBS=HIV Risk Taking Behavior Scale; MBM=Michigan Body Map 2011; MMSE=Mini Mental State Examination; NRS-I=Numeric Rating Scale of pain Intensity; PANAS=Positive and Negative Affect Schedule; PHQ-9=Patient Health Questionnaire; PMEQ=Prescription Medication Expectancy Questionnaire; SAOM-Consequences=Substance Abuse Outcomes Module—Consequences; SF-12=Medical Outcomes Study 12-Item Short-Form Questionnaire; SF-MPQ-2=Short-Form McGill Pain Questionnaire; SMQ=Synthetic Marijuana Questionnaire; STAI=State-Trait Anxiety Inventory; TLFB=Time Line Follow Back Interview; WHYMPI=West Haven-Yale Multidimensional Pain Inventory ; YACS=Yale Adherence and Competence Scale

* These assessments will be conducted at 3-, 6-, and 12-months *post-intervention*
**If a participant is unable (i.e. does not participate in the first follow-up) to complete this, he/she may be asked to do it at a subsequent assessment.

Pain tolerance. *(AMEN 24386)*-The ischemic pain task (IPT) is a frequently used measure of pain tolerance. This procedure involves performing hand grip exercises while the blood flow to the arm is obstructed through the use of a standard blood pressure cuff. In this procedure, the non-dominant arm of the subject is elevated above the heart for 30 seconds to allow for the blood to drain, after which a blood pressure cuff is positioned and inflated to 200 mm Hg. Subjects then are asked to perform hand grip exercises for a specified duration and effort level, and are instructed to continue until the pain becomes intolerable, but not in excess of a specified time (although we expect the cut-off to be 5 minutes, some of the literature has indicated a cut off time of 20 minutes [111-114]). This procedure is commonly used in research and does not present any short- or long-term risks to participants and is not expected to cause any lasting discomfort or side effects.

Urine samples will be collected to determine levels of amphetamines, methamphetamines, cocaine, THC (marijuana), and morphine (and/or opiates). Percent of urines positive for any of these substances during the follow-up month will be used to validate self-report measures of abstinence.

V. Data Management and Analysis

Data Management. The project's Data Manager will conduct all data management activities under the supervision of Drs. Ilgen and Kim. Data will be entered by research staff for the baseline and follow-up interviews using double entry. Data cleaning will be conducted throughout the data collection period to ensure the production of a final dataset for analysis at the end of data collection. SAS (Statistical Analysis System) will be used to examine and prepare data for the analysis. The raw data files, SAS data sets, and CD-ROMs will be secured at all times.

Sample Size Considerations. Sample size was calculated to have 80% power to detect a clinically meaningful and detectable effect size. We chose a between-group difference in time-averaged change in pain of 1.0 on a 0 to 10 scale as the minimal clinically meaningful change in pain intensity, and this is very close to what we observed in the pilot data which were collected in similar patients with only an intervention group

(mean change scores from baseline to 3 months = 1.05, SD of change scores = 2.21). A 1.0 point reduction in pain intensity seems to be a conservative meaningful time-averaged effect size to detect in this study, even after assuming some reduction in pain in the control group.

Using a conservative alpha of 0.01, a total of 180 participants (90 per treatment group) with complete data from baseline and 3 follow-up measurements will be needed in each gender to achieve 80% power to detect the time-averaged effect size within each gender. This assumes an average of 10 participants per treatment unit (cluster), a common SD of change of 2.21, a conservatively assumed intra-cluster correlation of 0.2, and a within-person variance of 1.0. The sample size calculation was done using Optimal Design for Multi-level and Longitudinal Research. Although we typically have follow-up rates of 85-90%, we will use a conservative estimate of 20% lost to follow-up, yielding 226 participants needed for each gender to detect the clinically meaningful size of the CBT effect in men as well as in women. The proposed sample size would provide adequate power to detect the CBT effect on other outcomes such as pain tolerance, alcohol and illicit drug use or opioid medication misuse as long as the effect size is approximately 0.45 (= 1/2.21) or larger. The secondary aims are designed to better understand the effects of the intervention on substance use and to examine important secondary treatment outcomes (HIV risk behaviors and depressive symptoms). Because of the exploratory nature of these analyses, we did not specifically power the study for their examination.

Primary Analytic Strategy. The study data will be nested within an intervention group where on average about 10 participants will be in the same session, and the data will also be longitudinal with a baseline and four follow-up assessments made over the course of one year. We will therefore use multi-level (mixed-effects) regression models to test all primary hypotheses [106]. For each outcome, a linear trajectory for each participant will be modeled using random intercepts, and CBT group indicator and assessment times in months will be included as primary independent variables. We will correct for family-wise error for all primary analyses. *To adjust for time in a controlled environment, we will first calculate the proportion of patients who re-entered any controlled environment at each follow-up time. We will examine the frequency of re-entry into a controlled environment and the distribution of time spent in the controlled environment and will consider various ways to handle time spent in a controlled environment, including the use of the cumulative time spent in a controlled environment after the discharge from the initial treatment episode as a time-dependent covariate in the longitudinal model.*

Prior to fitting a mixed-effects model for each hypothesis, a graphical exploration of the outcome variables will be done to examine the distribution of the outcome variables and, if the distribution is found to be highly skewed, we will consider appropriate transformation of the outcome variable in order to stabilize the variance. For each outcome, the model will allow estimation of various between-person parameters, but most importantly (a) the time-averaged average scores for both groups, (b) the average slope over time in the control group, and (c) the effect of the intervention on the average slope. An autoregressive covariance specification will be used first, but appropriateness of other covariance specification will also be considered.

Missing Data. To minimize missing data, we will make every effort to gather follow-up information for all participants. As described in Primary Analytic Strategy, the use of mixed effects regression to model individual trajectories will allow the use of data from all participants (not just completers) and provides unbiased parameter estimates that account for missing data under the missing-at-random assumption[107]. If our examination of the pattern of missingness suggests that the missing-at-random assumption is untenable, we will handle missing data with a pattern mixture model[108].

Specific Aim 1 (Hypothesis 1). *Participants randomized to the CBT intervention will report a greater reduction in pain, pain tolerance and pain-related disability at end-of-intervention (1-month) and 3-, 6-, and 12-month post-intervention follow-ups compared to participants randomized to the SPC (control) condition.* We will test this hypothesis separately by each gender, and for each outcome. We will use a linear mixed-effects model and estimate the treatment effect as the difference in the time-averaged changes from baseline in pain levels (using the NRS-I[81]) and in pain-related disability (using the Interference subscale of the WHYMPI [94]) over the course of the 1-year follow-up. Because reduction in pain is of primary interest, the analysis will model change-scores from baseline in the response variable as dependent variable, and the independent variables will include the baseline values of the response variable, time in months since randomization and the treatment group indicator. The parameter estimate of the treatment group indicator will estimate the time-averaged treatment effect. If the graphical exploration (described above) shows potentially differential linear decrease in pain over time, we will include an interaction of time by treatment group indicator to model and test for this.

Specific Aim 2 (Hypothesis 2). *Relative to the control condition, the CBT condition will significantly*

decrease alcohol use, illicit drug use and extent of opioid medication misuse at 3, 6, and 12 months post-intervention. Similar to Hypothesis 1, we will test this hypothesis separately by each gender, and for each outcome. We will first assess the distribution of measures collected to assess alcohol use, illicit drug use and opioid medication misuse to see if a summary or composite measure of each of these may represent the use or misuse more appropriately. For example, illicit drug use will be obtained as the number of days the participant used each of multiple drugs, and thus we may consider combining the days of any of the illicit drug use. We will also combine the alcohol and drug use data obtained using TLFB interviews as the percent days abstinent from alcohol and drugs during the past 30 days at each assessment time. We will then check the distribution of the substance use and opiate misuse measure (measured using COMM), and unless the data are highly skewed, we will use a linear mixed-effect model to test the hypothesis and to estimate the treatment effect as the difference in the time-averaged changes from baseline in these outcome measures over the course of the 1-year follow-up. It is important to note that at one-month which is immediately post-intervention, participants will still reside in the residential treatment center. During residency, it is unlikely that they will have any or notable substance use or misuse of medication. Thus, the main departure from the analytic plan for hypothesis 1 is that for hypothesis 2, we will compare the outcomes measured at 3, 6, and 12 months, but not at 1 month. The rest of the analytic plan will be similar to that of hypothesis 1 where, for example, we will use the linear mixed effects model to examine whether treatment group is associated with differences in the average trajectory of substance use (alcohol and drug use as measured by % days abstinent on the TLFB).

Secondary Aim 1 (Hypothesis 1). *Reduction in pain or pain tolerance from baseline to the end-of-intervention (i.e. the 1-month assessment) will mediate the effect of CBT on frequency of illicit drug and alcohol use and extent of opioid medication misuse at 3, 6 and 12 months.* We plan to use a series of mediational analyses following the procedures outlined by Baron and Kenny[109] and described in more detail by Kraemer and colleagues[110] to examine whether change in pain from baseline to 1-month assessment mediates the relationship between treatment and follow-up substance use. Specifically, we will first examine if treatment assignment predicts reductions in substance use. Secondly, we will examine if change in pain from baseline to 1-month predicts follow-up substance use. Finally, we will examine if the addition of change in pain from baseline to 1-month significantly diminishes the previously established relationship between treatment assignment and follow-up substance use.

Secondary Aim 2 (Hypothesis 2). *Increases in self-efficacy, motivation, effective coping and acceptance from baseline to end-of-intervention (i.e. the 1-month assessment) will mediate the effect of CBT treatment on frequency of illicit drug and alcohol use and extent of opioid medication misuse at 3, 6 and 12 months post-intervention.* Similar to the method for Secondary Aim Hypothesis 1, we will run each set of analyses separately for each potential mediator for illicit drug and alcohol use and for extent of medication misuse.

Secondary Aim 3 (Hypothesis 3). *Relative to the control condition, the CBT condition will significantly decrease HIV risk behaviors and depression at post-intervention, 3, 6, and 12 months post-intervention.* The analyses of this aim will be similar to Specific Aims 1 and 2, and HIV risk behaviors and depressive symptoms will be analyzed separately. The analyses will model change-scores from baseline in the response variable as the dependent variable, and the independent variables will include the baseline values of the response variable, time in months since randomization as well as the treatment group indicator. The parameter estimate of the treatment group indicator will give an estimate for the time-averaged treatment effect.

VI. Potential Risks, Minimizing Risks, and Potential Benefits

Potential risks and Minimizing Risks

The major potential risk to study participants is violation of confidentiality of assessment data and audiotaped sessions. The risk of violation of confidentiality exists because participants will be disclosing personal information, both in assessments and CBT sessions. This risk is related to the damage that could be caused by an inadvertent release of sensitive information (e.g., psychiatric symptoms, drug use). Participants will be informed of the procedures taken to protect their confidentiality. No questions will be asked pertaining directly to issues of child abuse. Because information will be obtained about acute suicidality, based on responses on the BDI and confirmed by in-depth assessment of participants by the research *staff,* the consent form will contain a statement explaining mandatory reporting requirements for information regarding intention to harm self or others (e.g., suicide, homicide) prior to participating in the study.

Participants may experience some physical discomfort from being exposed to the (AMEN 24386)-Ischemic Pain Task (IPT).. Participants will be asked to raise their arm above their heart to allow for the blood to drain, after which a blood pressure cuff is positioned and inflated to 200 mm Hg. Subjects then are asked to perform hand grip exercises for a specified duration and effort level, and are instructed to continue until the pain becomes intolerable. This procedure is commonly used in research and does not present any short- or long-term risks to participants and is not expected to cause any lasting discomfort or side effects. Participants are free to terminate this task at any time.

There is also a slight risk of psychological discomfort to study participants from the questions asked in the assessments. Participants may become anxious or uncomfortable as a result of being asked personal questions. The research associate conducting assessments will be trained to respond to this emotional distress and to refer the participant to appropriate resources as necessary. All participants are free to terminate the assessments at any time or refuse to respond to any questionnaire item.

In addition, there is a small risk that the CBT or SPC conditions might upset participants. To minimize this risk, intervention sessions will be conducted by experienced, master's level clinicians with intensive training and weekly supervision by the PI and Co-I in dealing with issues that may arise. Further, the project will utilize therapeutic approaches (i.e., either CBT or psychoeducation paired with support) that have been widely used in those with SUDs. The components of CBT and SPC are non-confrontational and include therapist empathy and respect. It has been the experience of the project's investigators that these approaches drastically diminish the risks associated with the study's interventions (i.e., emotional distress, reactivity). Still, unexpected events are always possible in behavioral intervention research.

Minimizing Risks

1. Loss of confidentiality (risk unlikely):

Several steps will be taken to minimize the risk of breaches of confidentiality. First, every effort will be made to ensure that study data are always confidential, in terms of staff training and data storage, so that data cannot be linked to a particular person. Training of staff will include information about the importance of confidentiality and techniques to maintain confidentiality of all information reported by research participants.

Unique identification numbers will be assigned to all participants who complete the assessments. Only the participant code will appear on assessment forms and abstracted audio taped forms. All data forms and assessments will be coded with this number, rather than with a name. Participants' names and other identifying information will be kept separately from study data on password-protected files on a secure server with restricted access and/or in a locked cabinet in a locked room; and only participants' unique ID number will be kept in the database on password protected file. All paper forms will be stored in locked file cabinets. Computer data files will be saved with passwords. Consent forms and "Subject Directory" sheets will be stored separately from data in locked cabinets, because they contain identifying information/ participant ID. Prior to data entry of follow-up information, all identifying information will be removed from follow-up assessments. Only the subject code number will be entered with the study data. Furthermore, we will apply for a Certificate of Confidentiality from the NIH to protect the confidentiality of our data from legal requests.

In addition, to ensure that the loss of confidentiality associated with participating in the CBT group sessions is minimized, we will discuss the need to maintain confidentiality at the outset of the group and provide guidance for all members about how to best ensure the confidentiality of the other participants. All participants in the group will be informed of the limits of confidentiality in group-based treatments during the initial informed consent procedure as well as the start of each group session.

2. Discomfort during Ischemic Pain Task (IPT) (risk likely):

The IPT does not present any short- or long-term risks to participants and is not expected to cause any lasting discomfort or side effects. The IPT will be described in detail during the process of obtaining informed consent and only participants who understand and agree to the IPT will be included. Participants will be informed that they can discontinue the task at any time. To ensure safety the IPT will be terminated immediately for any participant persisting past (AMEN 24386)-a specified amount of time (although we expect the cut-off to be 5 minutes, some of the literature has indicated a cut off time of 20 minutes[111-114]). Discomfort experienced during this task is expected to be brief and quickly dissipate after removal of the blood pressure cuff. If a participant becomes distressed, the research associate will intervene as appropriate (i.e. comfort the participant and/or seek assistance from the PI).

3. Discomfort during assessments (risk likely):

Because there is a small risk that participants may experience some distress when answering survey questions, participants will be made aware of their right to refuse to answer any questions that make them uncomfortable or that they do not wish to answer, and they will be informed of their right to withdraw from the study at any time without penalty. Additionally, interviewers will be trained to discuss any such issues and concerns if they arise.

4. Risks associated with CBT or SPC sessions (risk likely):

To minimize the risk of CBT or SPC sessions making participants uncomfortable or distressed, sessions will be run by trained therapists with experience conducting group interventions in vulnerable populations. In addition, the clinicians will have intensive training and weekly supervision by the PI and/or Co-I's in how to deal with issues that may arise. Minor difficulties will be handled in the group or after session by the study therapists. If patients report any serious adverse events during treatment they will be referred to their primary therapist at their treatment agency. Although patients at high risk for suicide will be screened out of the intervention, the possibility remains that participants will experience acute suicidality during the course of the intervention. Patients will be regularly monitored for suicidality by the group leaders and any acutely suicidal patients will be referred to their primarily providers or the crisis management team at their treatment agency.

Potential benefits: Psychosocial treatments for pain have been in use for many years and are generally regarded as safe and efficacious, especially in comparison to many of the available pharmacological options for treating pain.

CBT Condition Benefits: Typically, individual participants in the CBT condition will have the experience of receiving 8 sessions of a group specifically focused on the challenges of living with both pain and substance use disorders and will have the experience of learning about pain and receiving peer (and therapist) support for their experiences with pain and substance abuse. Additionally, participants in the CBT condition will learn potentially effective coping strategies for managing their pain. The CBT condition includes standard care SUD treatment at their treatment agency, and participants in the SPC condition will receive the same standard of care.

Supportive Psychoeducation Control Condition Benefits: The control condition sessions will match the CBT condition in terms of level of attention and the non-specific aspects of receiving support for pain and substance misuse. Specific content related to pain for the SPC group is similar to that which was used by Turner, Mancl and Aaron [68], modified to cover multiple pain conditions; content related to substance use will based on psychoeducational attention control treatment for alcoholism (PACT) [82], modified to cover other substances in addition to alcohol. This condition is intended to help patients to better understand the origins and consequences of pain and substance use in their life. However, topics related to psychological factors associated with pain and possible psychosocial coping mechanisms will not be a part of the formal content of the group. Thus, the group will not directly overlap with the content of the CBT group. Participants, however, will receive written referral information regarding services and community resources for men and women experiencing chronic pain which they might not receive during their standard SUD treatment. In sum, potential benefits for the research far outweigh the risks for the participants.

Importance of Knowledge to be Gained

Because, at the present time, treatment options for patients with SUDs and pain are so few and so closely associated with potential negative outcomes, the clear need exists for the examination of other methods to manage pain in these patients. If CBT for pain proves to be effective with associated reductions in the use of illicit substances this would represent a significant advancement for the field. This improvement could inform the treatment of pain in other SUD treatment clinics, both residential and outpatient, as well as the treatment of pain in patients with SUDs seen in other treatment settings. We believe this potential for benefits far outweighs the minimal risks associated with this study.

AMEN 27764: Prisoners in Research

We will not be directly recruiting participants who are currently incarcerated at jails and/or prisons. However, given the characteristics of our patient population (ex. those with chronic pain and substance use disorders, we

anticipate that some of our participants will be incarcerated at the time of follow-up. We will request certification through the Michigan Department of Corrections. Approval will include compliance with federal rules regarding the use of prisoners in research, as well as the guidelines set forth by the Michigan Department of Corrections. Specifically, participants will be informed that their decision to participate in the study will not affect their release date or parole eligibility. We will also inform the individual of the possible need to report (ex. harm to self or someone else) to appropriate authorities/personnel. As per the PI's discretion, a urine screen may not be performed for issues such as the results may not be kept confidential (ex. rules or regulations of the agency or institutional policy may prohibit (ex. prison)).

Inclusion of Children

Participants in this study will be 18 years old or older for several reasons. The study site does not admit anyone under 18 years old for residential substance use disorder treatment. Further, an intervention for adolescents would likely require involvement of parents/guardians and therefore would require a different approach and varying content than the intervention proposed in this study. Because of these differences, a separate study would be required to appropriately study cognitive behavioral therapy for co-occurring pain and substance use disorders in adolescents.

Inclusion of Women and Minorities

Based on statewide treatment admission data, 68% of patients in Substance Use Disorder treatment in Michigan are male and 66% are Caucasian (25% African American, 9% other minorities; SAMSHA, 2005). Although women make up approximately 33% of all patients treated in the non-detoxification residential services at the proposed study site, Community Programs, Inc (CPI), in Waterford, Michigan, the proposed study will recruit equal numbers of men and women. Our pilot data indicate that, compared to statewide data, slightly more men recruited from CPI will be non-Caucasian and somewhat fewer women will be non-Caucasian. Specifically, in our pilot data from CPI, 56% of men were Caucasian, 35% were African American and 9% were of another racial background (i.e., Asian, American Indian, Native Hawaiian or Other Pacific Islander). Women at CPI were: Caucasian (80%), African American (16%), or other (4%). Our prior research at CPI indicates that 14% of participants were Hispanic or Latino.

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